REMARKS

Summary of Changes Made

The Application was filed with 1 claim, and claims numbering up to 8 were later added. Presently, claims 1 and 2 are canceled, claim 8 is amended for clarity, and claims 9-13 are added. Support for the amendments can be found throughout the specification, for example, page 5, lines 4-5 and 21-23. Support for new claim 9 can be found at pages 34-36 of the specification. Support for claims 10-12 can be found at page 20, lines 22-23 of the specification, while support for claim 13 can be found in table 3 (page 23) of the specification as well as the other pending claims. Accordingly, claims 3-13 (11 claims) are pending in the application. No new matter has been added.

Claim Rejections – 35 U.S.C. 103(a) (Samour/Piasecki/Cooper)

Claims 1-5 and 8 have been rejected as allegedly being obvious over U.S. 4,861,764 to Samour, et al., ("Samour"), in view of Piasecki, et al., (Abstract of PL 175837; "Piasecki"), and U.S. 4,557,934 to Cooper, et al., ("Cooper").

Initially, The Examiner will note that claims 1 and 2 have been cancelled herein. Applicants respectfully submit that the present invention is non-obvious over Samour in view of Piasecki and Cooper, based on the following.

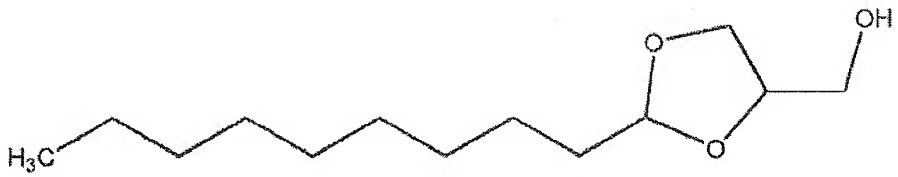
To properly determine a *prima facie* case of obviousness, the Examiner "must step backward in time and into the shoes worn by the hypothetical 'person of ordinary skill in the art' when the invention was unknown and just before it was made," M.P.E.P. 2142. Three criteria may be helpful in determining whether claimed subject matter is obvious under section 103(a): first, if there is some suggestion or motivation to modify or combine the cited references; second, if there is a reasonable expectation of success; and third, if the prior art references teach or suggest all the claim limitations, *KSR Int'l Co. v. Teleflex, Inc.,* 550 U.S. 398, 127 S.Ct. 1727 (2007). With regard to the first criterion, the mere fact that references an be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. In re *Mills,* 916 F.3d 690 (Fed. Cir. 1990). "Knowledge in the prior art of every element of a patent claim ... is not of itself sufficient to render the claim obvious," *Graham v. John Deere Co.,* 383 U.S. 1, 17-18 (1966); *Teleflex, Inc. v. Ficosa N. Am. Corp.,* 299 F.3d 1313, 1333-34 (Fed. Cir. 2002). The issue is whether there is an apparent reason

to combine the known elements in the fashion claimed by the patent at issue. *KSR Int'l Co. v. Teleflex, Inc.*

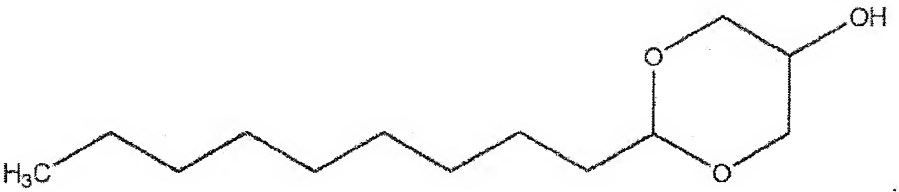
The present invention is directed to enhancing penetration of a pharmaceutically active substance across the blood-brain barrier, and not merely penetration through the skin as taught in the prior art. Medications are seen to act more rapidly with the claimed enhancers, and at least adequately at lower doses as compared to the prior art, as evidenced in table 3, page 23 of the specification. The instantly claimed method and composition involve activity at a location other than the administration of the composition. Table 3 shows antiparasitic activity on worm larvae in the brain of rats which were treated orally with mebendazole.

In particular, the invention relates to a method to improve permeation of a pharmaceutically active substance across a cell barrier, comprising co-administering the pharmaceutically active substance with a combination of two materials, that is, compound 1 and compound 2.

Compound 1:



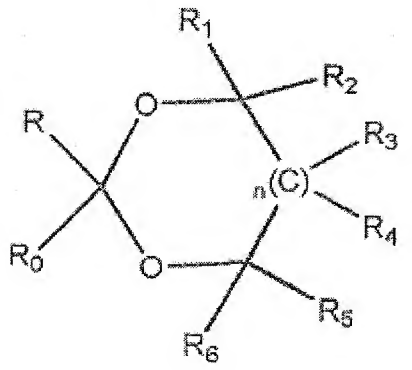
Compound 2:



The present application also relates to a composition to improve permeation of a pharmaceutically active substance across a cell barrier, the composition including compound 1 and compound 2, ad recited in claim 8. The instant claims further recite the method comprising co-administering compounds 1 and 2 in the ratio of about 9 : 1 (claim 4) and having an antibiotic or antiparasitic compound as the pharmaceutically active substance (claim 5).

The invention also relates to a method to improve permeation of a pharmaceutically active substance across the blood-brain barrier comprising co-administering the pharmaceutically active substance with compounds 1 and 2.

In contrast, Samour is directed to a therapeutic composition suitable for transdermal administration of a physiologically active agent, wherein the therapeutic composition includes a penetration enhancer as defined in the following formula:



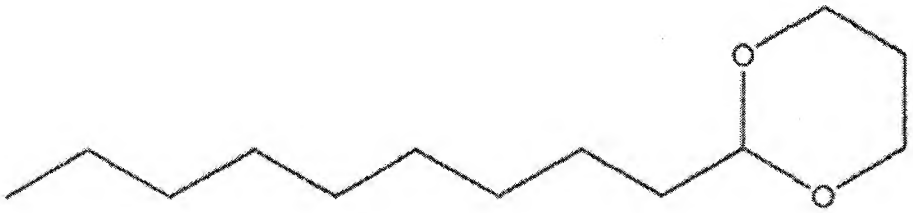
in which all the variables are defined therein.

Applicants respectfully submit that Samour fails to teach or suggest either compound 1 or compound 2, and further fails to disclose or suggest a method of co-administering compounds 1 and 2 with a pharmaceutically active substance, and further fails to disclose or suggest a composition including both compounds 1 and 2. Further, Samour fails to teach or suggest a method or composition where more than one permeation enhancer is used.

Despite the foregoing, the Examiner asserts that compounds of Samour and those instantly claimed have similar structures, and that would hence have the same properties and function in the same way, as noted on page 8 of the Office Action of 12 November 2008. In particular, the Examiner alleges that 2-n-nonyl-1,3- dioxolane (Samour's Example III) are structurally similar to instantly claimed compounds 1 and 2, and that "the same properties and function" can be expected. Applicants respectfully disagree.

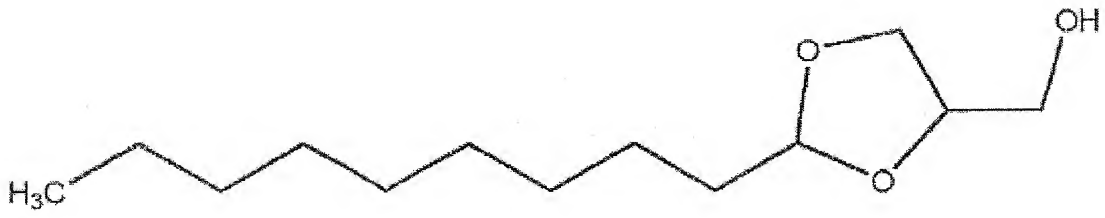
Applicants respectfully submit that Examples III and XIII are different types of compounds from instantly claimed compounds 1 and 2. As evidence of the dissimilarity, the structures of Samour's Examples III and XIII are provided for contrast:

2-n-nonyl-1,3-dioxolane (Example III),

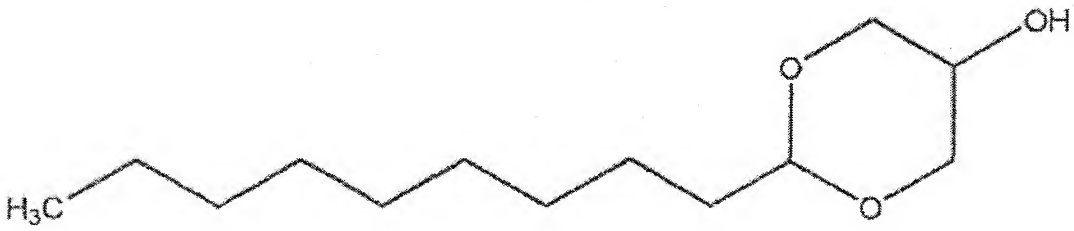


2-n-nonyl-1,3-dioxane (Example XIII)

while compounds 1 and 2 have the following chemical structures:



(2-nonyl-1,3-dioxolan-4-yl) methanol (Compound I)



2-nonyl-1,3-dioxan-5-ol (Compound 2)

As is evident from the above structures, Examples III and XIII are unsubstituted dioxolane or dioxane derivatives, while compound 1 is a hydroxymethyl-substituted dioxolane, while compound 2 is a hydroxyl-substituted dioxane. The skilled artisan would understand that compounds 1 and 2 are fatty alcohols, while Examples III and XIII lack a hydroxyl moiety.

Applicants also submit that the skilled artisan would expect the compounds of Examples III and XIII will exhibit different properties and functions from those exhibited by compounds 1 and 2. In particular, the two hydroxyl compounds (i.e., compounds 1 and 2) would be expected to have fundamentally distinct chemical properties, owing in large part to their increased polarity due to the hydroxyl groups. Indeed, instantly claimed compounds 1 and 2 will demonstrate a distinct amphiphilic nature, which the compounds of Examples III and XIII would lack.

Furthermore, Applicants submit that Samour utterly fails to teach or motivate any modification of the compounds (or delivery system) disclosed therein to arrive at the present invention. Samour fails to motivate the addition of the –OH or $-CH_2OH$ groups to the basic structures disclosed therein.

Further still, Applicants note that from the full teachings of Samour, only two hydroxyl compounds (Examples XI and XII) are even disclosed therein. These hydroxyl compounds are completely different in structures from compounds 1 and 2, a major difference being that they are unsaturated while compounds 1 and 2 are saturated. Indeed, these hydroxyl compounds are less favored by Samour, as evidenced by the fact that none of Samour's preferred compounds (that is, Examples III, IV, V, VI, VIII, XIII, XIV, and XV) include hydroxyl substituents, (col. 9, lines 20-24, and 50-65). As such, Samour clearly favors non-hydroxyl-substituted compounds as penetration enhancers, which is the reverse of the instant invention. Given these teachings or suggestions in Samour, a skilled artisan would conclude that Samour indeed teaches away from the instant invention.

Additionally, Applicants submit that the present invention has unexpectedly achieved surprisingly effective permeation effects compared to the permeation carriers of Samour. For example, instant Table 3 demonstrates that the presently claimed delivery systems' significantly increased permeation of mebendazole through the blood-brain barrier, resulting in an at least 16-fold improvement in reducing the worm infection at a dose of mebendazole reduced by more than 30-fold. In contrast, the best result offered by Samour was achieved with the compound of

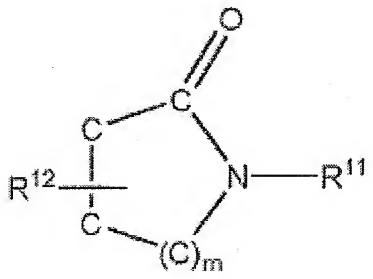
Example III as the enhancer, where an improvement of only about 8-fold was achieved with percutaneous Indomethacin absorption at the same dose (see col. 10 of Samour).

Finally, Samour's remaining test results show little permeation improvement. In view of Samour's disclosure, there is no reasonable expectation to a skilled artisan that the combination of two hydroxyl compounds (such as compounds 1 and 2) could possibly achieve a dramatically increased permeation of a medicament as disclosed only in the present application.

At least for the above reasons, the present invention is non-obvious over Samour. Applicants further submit that Piasecki and Cooper fail to cure the deficiencies of Samour.

Piasecki utterly fails to teach or suggest the use of compound 1, and therefore also fails to teach or suggest its use in combination with compound 2. Neither does Piasecki provide any motivation or suggestion to modify compound 2 to obtain compound 1, which would involve a ring-opening reaction, the stereochemistry of which would be quite specific, i.e., much more specific, than, say, a simple addition across a double bond or addition to the alkyl chain of, say, compound 1. Further, Piasecki fails to disclose any enhanced penetrating effect that compound 2 might possibly have, let alone co-administering compounds 1 and 2 for enhancing penetration effects, or formulating a composition containing compounds 1 and 2 to improve permeation. Indeed, the skilled artisan concludes that Piasecki teaches only ways to make compound 2, and nothing more. The mere existence of compound 2 as disclosed by Piasecki does not cure the deficiencies of Samour.

So too does the combination of Cooper fail to address the deficiencies in Samour and Piasecki. Initially Applicants note that Cooper utterly fails to teach or suggest the use of compound 1, and therefore fails to teach its combination with compound 2. Contrary to the Examiner's assertion at page 7 of the Action of 12 November 2008, Applicants respectfully submit that Cooper does not provide a general preference for binary combinations. Instead, Cooper teaches only specific binary systems that combine Azone with a diol, and/or certain N-substituted azacycloalkyl -2-ones, the general formula of which (including Azone) being as follows:



Clearly, N-substituted-azacycloalkyl-2-ones taught in Cooper arc lactams, which belong to a completely different class of compounds, with respect to compounds 1 and 2 as instantly claimed.

Thus, in view of Cooper's teachings, the skilled artisan would conclude that, apart from a discrete number of very specific binary penetration systems, unrelated to those instantly claimed, Copper fails to teach or suggest a general preference for binary penetration systems. Additionally Applicants note that Cooper fails to teach compound 2 or any compound with a similar structure for a binary penetration delivery system. Cooper simply fails to teach the skilled artisan any suggestion to combine compound 2 with any other compound, and in particular no suggestion to combine compounds 1 and 2. Only Applicants disclosure teaches the combination of compounds 1 and 2.

In summary, Applicants respectfully submit that: first, the cited art (i.e., Samour, Piasecki and Cooper) fails to teach or disclose compound 1 as an enhancer; second, there is absolutely no suggestion or motivation provided by Samour, Piasecki, and/or Cooper for modifying their compounds or delivery systems to arrive at the presently claimed invention, which requires a co-administration of compound 1 and compound 2; third, there would have been no reasonable expectation of success in achieving the present invention in absence of such teaching or motivation as above-discussed; and finally, the present invention has unexpectedly achieved surprisingly dramatic permeation effects in light of the teachings in the cited art. Therefore the present invention is indeed patentable over Samour in view of Piasecki and Cooper. At least for the above reasons, reconsideration and withdrawal of the rejections of the instant application over Samour in light of Piasecki and Cooper is respectfully requested.

Looking more closely at the cited prior art and other art of record, Cooper deals with topical treatments, Hui with local treatment of nail infections, Fuhrmann also with transdermal systems, and Samour with percutaneous absorption. The skin penetration enhancers such as those described in all cited references exhibit their activity mainly at the site they are applied, namely in the skin or the nails (see e.g., Hui). None of the references discloses or suggests an effect of the penetration through the blood-brain barrier. None of the references, further, discloses the use of compounds 1 and 2 as an enhancer.

Piasecki is directed to a process of preparation of cis- and trans- 2-alkyl 5-hydroxy 1, 3, dioxanes according to formulas 1 and 2 (front page) where n is from 7 to 13. The substances are disclosed as being intermediates in the preparation of surfactants, p. 1, lines 12-15 (the four lines after "***"). Piasecki fails to disclose a compound that is itself useful as a surfactant, contrary to the Examiner's contention.

Hence, the value of the Piasecki reference to the Examiner is to disclose the mere existence of such compositions with no teaching or motivation to use such compounds as penetration enhancers, and providing mo motivation for combination with the other references.

Certain dioxolane compounds disclosed in Samour are similar (but not identical) to the compounds A and B, namely the compound of Example XI and XIII. The same applies for the compound ND disclosed in Fuhrmann, However, Fuhrmann teaches away form the use of such dioxolanes as it discloses "2-1-(nonyl)-7,3 dioxolane was not considered a very active dermal or transdermal penetration enhancer for hydrocortisone." Further, it says that "therapeutic concentration levels were not obtained" (by using such dioxolane as enhancer), (Fuhrmann, page 204, right col., second para).

A combination of certain enhancers having a structure different from that claimed, which are described in various prior art references, does not render obvious the instantly claimed combination of compounds having a substantially different effect.

In order to further support the surprisingly high activity of the claimed combination of enhancers, the applicant has carried out tests using different enhancers. The results are attached as Appendix A, entitled "Comparison of the Effects of Various Enhancers in crossing the Blood-Brain Barrier," which is a translation of "Vergleiche zur Wirkung verschiedener Enhancer zur Öffnung der Bluthirnschranke," as provided by the Applicant.

The experiments were carried out as described in the specification using rats infected with *Angiostrongylos* worms and treatment with mebendazole. This is to provide the Examiner with additional data, as suggested in the Advisory Action of 14 April 2009. It will be understood that the claimed combination of enhancers (compounds 1 and 2) is the "9:1 blend of (2-nonyl-1,3-dioxolan-4-yl) methanol and 2-nonyl-1,3-dioxan-5-ol," also termed HERR 2489 in the original German. As can be concluded from the table, there were 58 surviving larvae in the infection control. Treatment with mebendazole alone had practically no effect on the larvae, there were still 56-58 larvae counted after treatment out of 60 originally applied. With most enhancers tested a reduction of larvae of 14 to 70 % was achieved, typically of about 50 %. However, by using HERR 2489 as the enhancer, that is, by applying the method of the invention, a reduction of larvae of 81 to 85 % could be achieved, which is considerably higher than the effects obtained with other enhancers.

In plain language, HERR 2489 alone or mebendazole alone gave the worst results (i.e., substantially no therapeutic effect relative to the control), but their use together gave the best results. This is the claimed invention.

This effect could not have been foreseen from the knowledge of the prior art, as, e.g., in Fuhrmann, dioxolanes are described as far weaker enhancers than others such as Azone.

It is believed that the specific arguments over the cited prior art as well as the additional data on the performance of the claimed compositions will serve to patentably distinguish the invention and overcome all rejections.

Claim Rejections – 35 U.S.C. 103(a) (Samour/Piasecki/Cooper/Grasela)

Claims 6 and 7 have been rejected as allegedly being obvious over Samour in view of Piasecki and Cooper and further in view of U.S. patent No. 5,837,289 to Grasela, et al., ("Grasela"). These claims are directed to a method to improve permeation of a pharmaceutically active substance comprising co-administering compound 1 and compound 2. The instant claims further recite that the antibiotic as the pharmaceutically active substance is fluoroquinolone (claim 6), or that the antiparasitic compound is mebendazole (claim 7). The arguments raised hereinabove are incorporated herein by reference at this point with respect to distinguishing the instant invention over the combined teachings of Samour, Piasecki and Cooper.

Grasela is cited only for the general proposition that two penetration enhancers can be used and that fluoroquinolone and mebendazole are pharmaceutically active.

Applicants respectfully submit that the combination of Grasela with the foregoing references fails to render the present invention obvious. Applicants note that Grasela fails to teach compound 1, and also does not teach a method of co-administering compound 1 and compound 2 with the specific pharmaceutically active substances. Further, Grasela does not teach or suggest any penetrating enhancer that has a similar structure to that of compound 1 or compound 2. Additionally, Grasela does not provide any suggestion or motivation to the skilled artisan in achieving the instant invention. Indeed, Grasela adds nothing to the teachings of Samour, Piasecki and Cooper. Therefore, the instant claims are patentable over Samour in view of Piasecki and Cooper and further in view of Grasela.

Conclusion

In light of the foregoing, it is respectfully submitted that the present application is in a condition for allowance and notice to that effect is hereby requested. If it is determined that the application is not in a condition for allowance, the Examiner is invited to initiate a telephone interview with the undersigned attorney to expedite prosecution of the present application.

If there are any additional fees resulting from this communication, please charge the same to Deposit Account No. 18-0160, Order No. GIL-18977.

Respectfully submitted,

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Appendix A

Comparison of the Effects of Various Enhancers in crossing the Blood-Brain Barrier

(translation of Vergleiche zur Wirkung verschiedener Enhancer zur Öffnung der Bluthirnschranke)

Model: *Angiostrongylus*/ Rat
Infection dose: 60 L_3-Larvae
Treatment with Mebendazole 0.33 mg/kg bodyweight
Medication: 5th, 6th, and 7th days post infection, oral

Medication Enhancer	Surviving Larvae
Mebendazole + hexyl diglycerol	18-26
Mebendazole + PEG-40 hydrogenated castor oil	38-51
Mebendazole + palmitoyl ascorbate	27-35
Mebendazole + 1, 2, 7, 8 octanetetrol	22-34
Mebendazole + octanoylglucamine	27-35
Mebendazole + 2-n-nonyl-1,3-dioxolane	25-26
Mebendazole + 2-n-dodecyl-1,3-dioxolane	23-30
Mebendazole + 9:1 blend of (2-nonyl-1,3-dioxolan-4-yl) methanol and 2-nonyl-1,3-dioxan-5-ol	9-11
9:1 blend of (2-nonyl-1,3-dioxolan-4-yl) methanol and 2-nonyl-1,3-dioxan-5-ol	57
Infection Control	58
Mebendazole alone	56-58

Vergleiche zur Wirkung verschiedenerEnhancer zur Öffnung der Bluthirnschranke

Modell: *Angiostrongylus* / Ratte
Infektionsdosis: 60 L_3-Larven
Behandlung mit Mebendazol 0,33 mg/kg KGW
Medikation: 5., 6., 7. Tag p.i., oral

Medikation / Enhancer	überlebende Larven
Mebendazol + Hexyl-G2	18-26
Mebendazol + Cremophor	38-51
Mebendazol + Palmitoylascorbat	27-35
Mebendazol + 1, 2, 7, 8-Octantetrol	22-34
Mebendazol + Octanoylglucamin	27-35
Mebendazol + HERR 1873	25-26
Mebendazol + HERR 2637	23-30
Mebendazol + HERR 2489	9-11
HERR 2489 allein	57
Infektionskontrolle	58
Mebendazol allein	56-58